

# Treatment of gonorrhoea in the female with fortified procaine penicillin plus probenecid and with spectinomycin

K. PANIKABUTRA

*Bangrak Hospital, Venereal Disease and Treponematoses Control Division, Department of Health, Bangkok, Thailand*

Increased resistance of the gonococcus to penicillin is much more common in South-East Asia and the Western Pacific Region of the World Health Organization than in most other areas (Willcox, 1970). In Bangkok, it was found that the less sensitive strains (requiring MIC of more than 0.15 unit/ml.) amounted to 48.4 per cent. in 1969, 59.4 per cent. in 1970 (Suvanamalik, 1971), and 71.9 per cent. in 1971 (Suvanamalik, 1972).

In the Far East and in South-East Asia, high failure rates in the treatment of gonorrhoea with penicillin have been reported in recent years (Holmes, Johnson, and Floyd, 1967) even after large doses. In Bangkok, there was some deterioration in the results of treatment of uncomplicated gonorrhoea using a routine dosage of single injections of 4 m.u. fortified procaine penicillin, with increase in the failure rate from 12.5 per cent. in 1970 (Panikabutra and Suvanamalik, 1973) to 15.5 per cent. in 1971 (Panikabutra, 1973).

In December, 1971, a Regional Symposium on the Epidemiology and Control of Venereal Diseases was held in Bangkok under the auspices of the Regional Office for South-East Asia of the World Health Organization and it was decided that the schedule of treatment of uncomplicated gonorrhoea should be changed. The new schedule proposed was a combination of probenecid with the same dosage of fortified procaine penicillin. In patients in whom there was known to be sensitization to penicillin, it was suggested that a single injection of 2 g. spectinomycin dihydrochloride should be substituted.

The present study has been undertaken to evaluate the efficacy of these new treatment schedules when used as routine treatment for uncomplicated gonorrhoea in females at the Bangrak Hospital, Bangkok.

## Material and methods

### *Patients*

The treatment was given to 513 unselected female patients with uncomplicated gonorrhoea attending the clinic in the period January 1, 1972, to February 28, 1973. All the women were married and were of Thai nationality. The

age distribution is shown in Table I.

TABLE I *Age distribution of 513 cases*

<i>Age group (yrs)</i>	<i>No. of cases</i>
15-19	86
20-24	215
25-29	112
30-34	58
35-39	29
40-44	3
45-49	7
50 and over	3

### *Diagnosis*

This was based on the finding of Gram-negative intracellular diplococci in the stained smears and on the results of cultures of specimens taken from the urethra, the cervix, and, in most cases, the rectum. Blood for routine serological tests for syphilis was taken in every case.

Smears from the urethral, cervical, and rectal secretions were stained with Gram's stain and examined in the clinic.

Specimens from the urethra, cervix, and rectum were sent to the laboratory in Stuart's transport medium where they were transferred to a selective growing medium (Thayer-Martin).

Rectal tests were done in 493 cases out of 513. The tests were omitted only for those patients who refused permission.

Some of the gonococci isolated by culture were tested for sensitivity to penicillin by a plate-dilution method as part of the laboratory routine from July, 1972, onwards and some were tested by a diffusion method for sensitivity to spectinomycin dihydrochloride pentahydrate (Trobicin-Upjohn). All the patients included in this investigation had positive results to cultures. Those who admitted sexual exposure before the first follow-up examination within 2 weeks of treatment were excluded from the final assessment.

If gonococci persisted or reappeared within 14 days of treatment and if further intercourse was denied by the patient, then the treatment was considered to have failed; the reappearance of gonococci after 14 days, irrespective of the patient's history, was considered to be due to re-infection.

### *Treatment*

The study consisted of two series of patients:

**SERIES A** Probenecid 1 g. was given orally 1 hour before a single intramuscular injection of 4 m.u. fortified procaine

penicillin (PPF) (consisting of three parts aqueous procaine penicillin G to one part benzyl penicillin).

**SERIES B** A single injection of 2 g. spectinomycin dihydrochloride pentahydrate was given intramuscularly.

#### Follow-up

Follow-up visits were arranged for the day following treatment and 4 days, 7 days, 10 days, 14 days, 1 month, 2 months, and 3 months after treatment, but needless to say patients did not always attend exactly as requested. Specimens for smears and cultures were taken from the urethra and cervix on each occasion and from the rectum in most cases. Routine serological tests were performed at monthly intervals for 3 months. As was to be expected, only a small proportion of the patients (20 per cent.) completed this routine.

### Results

#### SERIES A

There were 372 patients in this series; 33 defaulted immediately after treatment and four admitted sexual exposure with their as yet untreated husbands before the first follow-up examination (on the 1st, 3rd, 7th,

and 10th day respectively). Thus there were 335 cases left for assessment. There were no failures in this series.

#### SERIES B

This consisted of 141 patients; nine defaulted immediately after treatment and none admitted exposure before the first follow-up examination. Thus 132 cases were left for assessment. There was only one failure with the treatment (0.7 per cent.).

A summary of the results obtained is given in Table II.

Details of follow-up and apparent results of treatment are shown in Tables IIIA and IIIB.

### Bacteriological results

#### SERIES A

The minimum inhibitory concentration (MIC) of penicillin for 31 of the strains was determined. Five of the strains (16 per cent.) were fully sensitive. The remaining 26 (84 per cent.) were less sensitive (Table IV).

TABLE II Results obtained with two treatment schedules

Schedule	Drug	No. treated	No. assessed	Result				No. defaulting after treatment	Re-exposure before first follow-up
				Cured	Not cured <sup>a</sup>	Relapse <sup>b</sup>	Re-infection <sup>c</sup>		
A	Probenecid 1 g. + PPF 4 m.u.	372	335	335	0	0	53	33	4
B	Spectinomycin 2 g.	141	132	131	1 (0.7%)	0	22	9	0

<sup>a</sup>Gc positive at first follow-up test and denied sexual intercourse

<sup>b</sup>Gc negative followed by Gc positive tests, within first 2 weeks and denied sexual intercourse

<sup>c</sup>Gc negative followed by Gc positive tests and admitted sexual intercourse

TABLE IIIA Follow-up and apparent results of treatment

Follow-up	No. of tests after treatment	Total cases		Findings					
				Cured		Not cured		Re-infection	
		Probenecid + PPF	Spectinomycin	Probenecid + PPF	Spectinomycin	Probenecid + PPF	Spectinomycin	Probenecid + PPF	Spectinomycin
(1) Observed less than 3 wks	1	33	8	33	7	0	1	16	8
	2	32	19	32	19	0	0		
	3	37	16	37	16	0	0		
	4	18	13	18	13	0	0		
	5	3	2	3	2	0	0		
(2) Followed-up for at least 3 wks	1	8	0	8	0	0	0	37	14
	2	18	1	18	1	0	0		
	3	48	4	48	4	0	0		
	4	48	19	48	19	0	0		
	5	43	27	43	27	0	0		
	6	39	15	39	15	0	0		
	7	8	6	8	6	0	0		
	8	0	2	0	2	0	0		
(3) Followed-up for 3 mths (included in 2 above)	2	2	1	2	1	0	0	5	2
	3	8	1	8	1	0	0		
	4	12	1	12	1	0	0		
	5	15	10	15	10	0	0		
	6	20	8	20	8	0	0		
	7	8	6	8	6	0	0		
	8	0	2	0	2	0	0		
Total		335	132	335	131	0	1	53	22

TABLE IIIB *Re-infections—Number of negative tests between treatment and the time re-infection was diagnosed*

Time re-infection noted after treatment (days)	Number of previous negative tests											
	Probenecid + PPF						Spectinomycin					
	1	2	3	4	5	6	1	2	3	4	5	6
8	1	2	—	—	—	—	2	1	—	—	—	—
10	—	1	—	—	—	—	1	2	—	—	—	—
12	—	2	—	—	—	—	—	—	—	—	—	—
15	1	3	1	2	—	—	—	2	—	—	—	—
16	—	—	1	—	—	—	—	—	—	—	—	—
17	1	1	—	—	—	—	—	—	—	—	—	—
21	—	3	—	1	—	—	—	—	—	—	—	—
25	—	1	1	—	—	—	—	—	—	—	—	—
30	2	3	3	2	1	—	—	1	1	1	—	—
45	1	2	—	2	—	—	—	—	—	—	—	—
60	—	3	3	2	2	—	—	1	4	3	1	—
90	—	—	2	2	1	—	—	—	—	—	1	1
Total	53						22					

## SERIES B

The MIC of spectinomycin dihydrochloride was determined in only seven cases (Table V).

Table VI shows the sites from which *N. gonorrhoeae* was isolated in 493 cases in which the rectal tests were performed.

## SIDE-EFFECTS

Patients with a history of penicillin allergy were not given this drug. Even so, of the 372 patients in Series A, eight developed anaphylactic reactions 5 to 25 minutes after the intramuscular injection. They

manifested sweating, respiratory distress, fall in blood pressure, and collapse. All recovered. One patient developed a generalized papular eruption 15 days after the injection. No side-effects were attributed to probenecid.

No side-effects occurred among the patients treated with spectinomycin.

## Discussion

Probenecid impedes the excretion of penicillin from the body and thus produces a higher serum concentration of the drug and prolongs its effect. The

TABLE IV *Minimum inhibitory concentration (MIC) of benzyl penicillin for 31 strains of N. gonorrhoeae*

MIC of penicillin G (unit/ml.)	No. of strains	Follow-up cases		Failure rate	Not followed up	Re-exposure before first follow-up examination
		Cured	Not cured			
Sensitive						
0.01	2	2	0		0	0
0.05	1	0	0		0	1
0.1	1	1	0	0	0	0
0.15	1	0	0		1	0
Less sensitive						
0.2	2	2	0		0	0
0.3	8	8	0		0	0
0.4	1	1	0		0	0
0.5	2	2	0	0	0	0
0.7	4	4	0		0	0
1.0	4	4	0		0	0
2.0	1	1	0		0	0
Over 2.0	4	4	0		0	0
Total	31	29	0	0	1	1

TABLE V *Minimum inhibitory concentration (MIC) of spectinomycin for seven strains of N. gonorrhoeae*

MIC of spectinomycin (μg./ml.)	No. of strains	Result		MIC of penicillin G (unit/ml.)
		Cured	Not cured	
0.25	1	1	0	0.01
2.0	1	1	0	0.4
Over 2.0*	4	4	0	One strain 0.1, three other strains not done
20.0	1	1	0	Over 2.0
Total	7	7	0	

\*precise level not determined

single intramuscular injections of 4 m.u. PPF combined with probenecid proved fully effective in the treatment of uncomplicated gonorrhoea in females. No failures were detected in this series.

According to Epstein (1959), about 5 per cent. of patients from United States troops in Inchon, Korea, who attended VD clinics showed hypersensitivity to penicillin. An earlier study (Panikabutra, 1973) showed that 2.4 per cent. of patients attending a VD clinic in Bangkok were sensitized to penicillin and the present study indicates a similar incidence. So even though penicillin is still regarded as the drug of choice in the treatment of gonorrhoea, it is important to have an alternative drug which is equally effective in cases of hypersensitivity to penicillin.

Spectinomycin was the alternative drug used in this study. Cornelius and Domescik (1970) reported that single doses of 2 g. spectinomycin yielded a 100 per cent cure rate in the cases of 108 men and 28 women. Reyn, Schmidt, Trier, and Bentzon (1973) studied the results in 113 patients (52 females and 61 males) treated with spectinomycin dihydrochloride, 2 g. in males and 4 g. in females. There was one failure among the 109 cases left for assessment. Stratigos, Marsellou-Kinti, Kassimatis, and Daikos (1973) found one failure among 65 men each treated with 2 g. spectinomycin.

In the present study, there was only one failure in 131 cases (0.7 per cent.); this suggests that spectinomycin dihydrochloride is a fully adequate substitute for the remedy of choice.

In these cases gonococci were more frequently found in the cervix than in the urethra as shown in Table V. Involvement of the ano-rectal region is said to occur in over 40 per cent. of females with gonorrhoea (King and Nicol, 1969). Olsen (1971) reported rectal involvement in 63.7 per cent. of such cases and Reyn and others (1973) reported 37 per cent. The fact that in this series gonococci were found in the rectum in 23.7 per cent. (117 out of 493) and that there were nine patients in whose cases gonococci were found only in the rectum indicates that rectal tests should be done if possible.

## Summary

513 cases of uncomplicated gonorrhoea in females with positive results to cultures were treated with

two regimens of treatment between January 1, 1972, and February 28, 1973, at the Department for Females, Bangrak Hospital, Bangkok. The highest incidence was found in the age group 20 to 24 years (215 out of 513). The patients were divided into two groups. In the first, probenecid 1 g. was given orally 1 hour before an intramuscular injection of 4 million units fortified procaine penicillin, and in the second an intramuscular injection of 2 g. spectinomycin dihydrochloride was given. 335 cases were followed in the first group and there were no failures; 132 cases were followed in the second group and there was one failure (0.7 per cent.). The fact that gonococci were found in the rectum in 23.7 per cent. of cases (117 out of 493) indicates that rectal tests are of considerable importance and should be included in the routine investigations.

There was no evidence that gonorrhoeal infection of the rectum was more resistant to treatment than infection at other sites.

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TABLE VI Sites where gonococci were found in 493 cases in which rectal tests were also taken

Site	Positive in three sites	Positive in two sites			Positive in one site			Total positive	
		219	9	15	49	108	9	No.	Per cent.
Urethra	+	+	+	—	+	—	—	361	73.2
Cervix	+	+	—	+	—	+	—	426	86.4
Rectum	+	—	+	+	—	—	+	117	23.7
No. of patients	84	243			166			493	100